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BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte ANNE DOUWE DE BOER,
MICHÃEL JOHANNES MARCUS EBSKAMP,
SIMON ALBERTUS LANGEVELD, IVO LAROS, and
MIRANDA DEBORA VAN DE RHEE[1]

Appeal 2014-009767
Application 12/933,083
Technology Center 1600

Before CHRISTOPHER G. PAULRAJ, TAWEN CHANG, and
DEVON ZASTROW NEWMAN, *Administrative Patent Judges*.

CHANG, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134(a) involving claims to methods for identification of genomic DNA in an organism, which have been rejected as obvious. We have jurisdiction under 35 U.S.C. § 6(b).

We REVERSE.

STATEMENT OF THE CASE

According to the Specification,

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[1] Appellants identify the Real Party in Interest as Expressive Research B.V. (Appeal Br. 1.)

> [t]he size of eukaryotic genomes ranging from a few tens to several hundreds of megabases is . . . still beyond the capacity of current high throughput sequencing technologies. Furthermore, the vast majority of genomic DNA in eukaryotic organisms, . . . provides no valuable information . . . as it is never expressed and therefore does not seem to contribute to expression of traits. Therefore, to identify molecular markers, methods that focus on those parts of a genome that are more prone to reveal molecular markers closely linked to traits have an advantage over methods which analyse just random selections from genomes including non-expressed areas.

(Spec. 1:26–2:7.) Further according to the Specification, the methods of the invention "make[] it possible to determine sequences in a selected part of the genomic DNA representing the coding regions of the majority of expressed genes and their surroundings." (*Id.* at 2: 8–11.) The Specification states that "[c]omparison of such selected parts between different individuals allows identification of polymorphic sites that are inside or in close vicinity of expressed genes" and that, "[s]ince frequency of polymorphisms is higher in non-coding regions, more polymorphisms can be related to expressed genes." (*Id.* at 2:11–25.)

Claims 2–12 and 16–21 are on appeal. Claim 17 is illustrative and reproduced below:

> 17. A method for the identification of genomic DNA in an organism, comprising
>
> a) providing a library of single stranded cDNA fragments that are coupled to beads through a linker that comprises an affinity ligand and a primer-recognition site;
>
> b) hybridizing single stranded genomic DNA (gDNA) fragments with said single stranded cDNA fragments, wherein said gDNA fragments comprise at least one adaptor to provide a primer recognition site, wherein the gDNA fragments are longer than the cDNA fragments,
>
> c) extending said hybrids with polymerase,
>
> d) amplifying said hybrids, and

> e) high throughput sequencing said hybrids,
> wherein said single stranded gDNA fragments have been obtained by isolating gDNA from an organism and preparing from said gDNA single stranded gDNA fragments ligated to adaptors, and
> wherein the single stranded cDNA fragments have been obtained by isolating mRNA from the same or a different organism and preparing from said RNA single stranded cDNA fragments with one adaptor containing an affinity ligand.

(Appeal Br. 13 (Claims App'x).)

The Examiner rejects claims 2–12 and 16–21 under 35 U.S.C. § 103(a) as being unpatentable over Gnirke,[2] Ruan,[3] and Hodges.[4] (Ans. 2.)

DISCUSSION

Issue

The Examiner has rejected claims 2–12 and 16–21 under 35 U.S.C. § 103(a) as obvious over Gnirke, Ruan, and Hodges. The Examiner finds that

> Gnirke discloses "providing a library (also called "pool" or "collection" of single stranded cDNA fragments which are 'capture baits' . . . and contemplate coupling these cDNA fragments/bait sequences to a linker that comprises an affinity ligand, preferably biotin, which is then intended to be coupled to streptavidin beads.

(Ans. 3.) The Examiner finds that Gnirke discloses "adding the 'bait' oligonucleotides to a pool ('pond') of genomic DNA fragments containing universal adapters, performing hybridization in solution of the 'bait' oligonucleotides with the genomic fragments containing the universal adaptors, performing hybrid capture." (*Id.* at 3–4 (citation omitted).)

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[2] Gnirke et al., US 2010/0029498 A1, published Feb. 4, 2010.
[3] Ruan et al., US 2006/0084083 A1, published Apr. 20, 2006.
[4] Emily Hodges et al., *Genome-wide in situ exon capture for selective resequencing*, 39 NATURE GENETICS 1522 (2007).

The Examiner finds that Ruan generally discloses a method of creating a linked tag comprising a terminal transcribed sequence of a gene as well as "a method for identification of genomic DNA by mapping back to chromosomal DNA (also called genomic DNA or gDNA) in an organism using cDNA." (*Id.* at 4; *see also id.* at 6–7.) In particular, the Examiner finds that Ruan discloses "isolating mRNA from a selected organism and preparing from the mRNA small single stranded cDNA fragments with one adaptor containing a biotin affinity label" as well as a method of creating 3' end biotinylated cDNA immobilized on streptavidin coated magnetic beads. (*Id.* at 6–7.) The Examiner also finds that Ruan discloses "isolating genomic DNA from the same or a related organism and preparing from said genomic DNA single stranded genomic DNA fragments ligated to adaptor molecules." (*Id.* at 7.) The Examiner further emphasizes that Ruan suggests that its method can be used in combination with other genomics techniques, such as parallel sequence analysis. (*Id.* at 5–6.) The Examiner therefore finds that Ruan suggests the steps in the method of claim 17 because Ruan discloses "using immobilized short sequences as bait to capture genomic sequences which can then be amplified and sequenced on a high throughput basis." (*Id.* at 4; *see also id.* 7 and 8.)

The Examiner finds that Hodges discloses "a method of capturing genomic sequences using a library of shorter single stranded exonic DNA sequences which meets the limitation of providing a library of single stranded cDNA fragments." (*Id.* at 9.) In particular, the Examiner finds that Hodges discloses a method comprising fragmenting genomic DNA; repairing, blunting, and phosphorylating the ends of such DNA and ligating linkers; denaturing the strands and capturing said DNA with arrayed probes

of exonic DNA sequences; and recovering the selected genomic fragments by elution, lyophilization, and PCR enrichment. (*Id.*) The Examiner also finds that Hodges discloses high-throughput sequencing. (*Id.*) Finally, the Examiner finds that Hodges suggests "using sequences *other than* exon sequences to capture genomic regions." (*Id.* at 10.)

The Examiner concludes that a skilled artisan

> would have been motivated to combine the elements of Gnirke [] and Ruan [] and Hodges [] using a library of cDNAs as a capture mechanism for genomic sequences, for the rationale provided by Gnirke [] that "[s]election as described herein dramatically simplifies large-scale exon resequencing by avoiding the need to amplify hundreds of thousands of exons from each DNA sample" and that " . . . the procedure can be made to work at significant scale using cDNA clones as capture baits[.]"[]
>
> It would have been obvious to one of ordinary skill in the art . . . to combine the . . . solution hybridization, bait-capture cloning methods of Ruan [] for the purpose of using a library of cDNA as a capture mechanism for genomic sequences as explicitly disclosed by Gnirke [] in combination with the computer/automated sequencing software analysis of Hodges and Ruan [] because Ruan [] disclose[s] using cDNA as hybridization bait, disclose[s] using cDNA to map back to corresponding chromosomes . . . , and because the cited references show successful employment of the presently claimed methods of solution hybridization, biotin-avidin solid support bead capture, and use of rare recognition sites and respective enzyme cutters, all of which were known and were successfully used in the art of cloning, solution hybridization, and cDNA library construction and screening.

(*Id.* at 11.) The Examiner further concludes that,

> "[a]bsent evidence to the contrary, in view of the high skill level of one of ordinary skill in the art, . . . it is considered that one of ordinary skill in the art would have had a reasonable expectation of success . . . to use a library of cDNA as a capture mechanism for genomic sequences to arrive at the presently claimed invention (especially in view of Hodges . . . stating that "[o]verall, the methodologies that we

> present allow a sensible approach to disease-focused resequencing projects, and we hope that they will expand the capacity of individual investigators or small consortia to efficiently detect new disease-causing mutations").

(*Id.* at 11–12.)

Appellants concede that "each individual step [of the claims] can be performed by the skilled artisan," but contend that "what is new in the claimed invention is the arrangement of the steps." (Appeal Br. 6.) Appellants contend that "[t]he claimed protocol is not an arbitrary arrangement of steps, but rather a specific sequence designed to maximize the success of identification of genes including exons and introns and noncoding sequences of all sorts." (*Id.* at 7.) Appellants contend that "[t]he Examiner has not made a case that there is a logical way to combine the teachings of the three cited documents to result in the specific protocol that is being claimed." (*Id.* at 4; Reply Br. 4–5.) Among other things, Appellants also dispute the Examiner's characterization of Ruan (Appeal Br. 9; Reply Br. 6–8), and further argue that none of the cited references "discloses the step of extending a hybrid containing a captured genomic DNA and smaller bait cDNA fragment with polymerase (step (c) in claim 17 . . .)" (Reply Br. 3).

The issue with respect to this rejection is whether the evidence of record supports the Examiner's finding that the claims are obvious over the combination of Gnirke, Ruan, and Hodges.

Analysis

In response to Appellants' argument that the Examiner has not sufficiently articulated a reason for combining the teachings of the cited references to arrive at the claimed protocol, the Examiner contends that

"[a]ll of the elements of the presently claimed invention are disclosed in the combination of cited references." (Ans. 13.) The Examiner also contends that a skilled artisan would have been motivated to combine the elements of the references to arrive at the claimed invention because Gnirke teaches that its method "dramatically simplifies large-scale exon resequencing by avoiding the need to amplify hundreds of thousands of exons from each DNA sample" and "can be made to work at significant scale **using cDNA clones as capture baits**." (*Id.* at 16; *see also id.* at 13.) The Examiner further contends that a skilled artisan would find it obvious to combine the various disclosures of Gnirke, Ruan, and Hodges because (1) Ruan discloses using cDNA as hybridization bait and mapping cDNA back to corresponding chromosomes and (2) the cited references show that the various techniques recited in the presently claimed methods are all known and have been successfully employed in the relevant art. (*Id.* at 13.)

We find Appellants have the better argument. An invention "composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art. . . . [I]t can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." *KSR Int'l v. Teleflex Inc.*, 550 U.S. 398, 418 (2007). In this case, while the Examiner has pointed to disclosures in the cited references of techniques recited in the claims, the Examiner has not explained why a skilled artisan would pick and choose the steps disclosed in the cited references and combine them to arrive at the

particular claimed methods.[5] Gnirke's disclosure that its method simplifies large-scale exon resequencing and can be made to work at significant scale using cDNA clones as capture baits does not, without more, provide a reason for combining its teachings with those of Ruan and Hodges, or for modifying Gnirke's method with the techniques disclosed in Ruan and Hodges to arrive at the claimed method, which requires more than using cDNA clones as capture baits. For instance, it does not explain why a skilled artisan would hybridize single stranded cDNA fragments with longer gDNA fragments and then extend such hybrids with polymerase prior to amplification and high-throughput sequencing. (Reply Br. 3.) The Examiner states that "Ruan . . . disclose[s] extensive methods for using adaptors to provide primer recognition sites for extending with polymerase, amplifying the hybrids, and high throughput sequencing." (Ans. 17–18.) However, the Examiner has not identified a disclosure in Ruan where an incomplete cDNA/gDNA hybrid is extended with polymerase. Likewise, while it is not disputed that "the possibility of extending incompletely paired hybrids with polymerase is known" (Reply Br. 3), the Examiner has not articulated how the cited art in combination suggests using such an extension to identify genomic DNA in an organism.

The Examiner further responds that "the test for obviousness is not whether the features of a secondary reference may be bodily incorporated

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[5] We note that "[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR*, 550 U.S. at 416 (2007). On the record before us, however, the Examiner has not established that the claimed method is no more than "the predictable use of prior art elements according to their established functions." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 417 (2007).

into the structure of the primary reference" or whether the claimed invention is "expressly suggested in any one or all of the references," but rather "what the combined teachings of the references would have suggested to those of ordinary skill in the art." (Ans. 16.) While we agree with the Examiner's general articulation of the law, we are not persuaded by the Examiner's response. "[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *KSR,* 550 U.S. at 418. Thus, while the Examiner need not show that the features of Gnirke, Ruan, and Hodges may be "bodily incorporated" into the other references' methods or show that the claimed invention is "expressly" suggested by the cited references, the Examiner still must articulate some reasoning as to how or why the combined teachings of the references would have suggested the claimed method to a skilled artisan.

Finally, the Examiner argues that Ruan "meets . . . many of the dependent claim limitations [and] is clearly a relevant reference to one of ordinary skill in the art of bait/capture nucleic acid hybridization." (Ans. 19.) Citing paragraphs 68, 184, and 186, the Examiner further argues that, with respect to steps (a) through (e) of claim 17, Ruan "disclose[s] using immobilized short cDNA sequences as bait to capture genomic sequences which can then be amplified and sequenced on a high throughput basis." (*Id.* at 19–20.) The Examiner also emphasizes that "Ruan . . . explicitly suggests combining [its] techniques with other genomics techniques." (*Id.* at 19.) It is unclear which elements within the cited Ruan paragraphs the Examiner relies on to meet the limitations in steps (a) through (e) of claim

17.[6] In any event, while Ruan may be analogous art, the Examiner has not articulated a sufficient reason why a general statement regarding combination with other genomics techniques suggests combining Ruan's teachings with the particular techniques taught in the other cited references, in the order specified, to arrive at the claimed invention.

SUMMARY

For the reasons above, we reverse the Examiner's decision rejecting claims 2–12 and 16–21 under 35 U.S.C. § 103(a) as obvious over Gnirke, Ruan, and Hodges.

REVERSED

[6] Paragraph 68 discloses immobilized cDNA fragments; however, this appears to be in the context of creating cDNA tags rather than using fragments as bait to capture genomic sequences. (Ruan ¶ 68.) Paragraphs 184 and 186 disclose that the tags can be hybridized with oligonucleotides (*e.g.*, "every possible permutation of a 10-mer") immobilized on a solid support, for instance in the context of parallel sequence analysis. (*Id.* at ¶¶ 184 and 186.) However, paragraphs 184 and 186 appear to disclose immobilizing oligonucleotides rather than cDNA fragments, and also do not appear to disclose using cDNA as "bait" to capture genomic sequences. To the extent the Examiner's position is that these disclosures suggest or render obvious "using immobilized short cDNA sequences as bait to capture genomic sequences which can then be amplified and sequenced on a high throughput basis," the Examiner has not sufficiently articulated his reasoning.